

# Serum myoglobin for the early non-invasive detection of coronary reperfusion in patients with acute myocardial infarction

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The ideal non-invasive method for detecting coronary reperfusion has not yet been established. In 63 patients with acute myocardial infarction, serum myoglobin and creatine kinase-MB were measured every 15 min. Thrombolytic treatment was given ( $n=52$ ) and acute coronary angiography showed a patent infarct-related artery in 49 patients while 14 patients had no coronary reperfusion. Median time to peak serum myoglobin was shorter (reperfusion group 178 min vs no reperfusion group 480 min,  $P<0.0001$ ) than time to peak serum creatine kinase-MB (reperfusion group 550 min vs no reperfusion group 1080 min,  $P<0.0001$ ),  $P<0.0001$ . Myoglobin appearance rate, calculated as the concentration at 2 h divided by baseline values ( $Mb_2/Mb_0$ ) was highest in the reperfusion group (4.0 vs 1.6),  $P<0.001$ .

An earlier proposed index,  $Mb_2/Mb_0 > 2.4$  for identification of reperfusion 2 h after thrombolytic therapy, showed pre-

dictive values of positive and negative tests of 0.94 and 0.44, respectively. Combining this index with signs of medium to larger infarct size ( $Mb_2 > 200 \mu\text{g} \cdot \text{l}^{-1}$ ) increased the predictive value of the negative test to 1.00. In patients with signs of minor infarcts ( $Mb_2 < 200 \mu\text{g} \cdot \text{l}^{-1}$ ) the predictive values of positive and negative tests were 0.94 and 0.79, respectively, 5 h after onset of thrombolytic therapy.

An early rise and a peak in serum myoglobin values seems to be a reliable and simple non-invasive indicator of successful and unsuccessful reperfusion therapy.

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**Key Words:** Acute myocardial infarction, intravenous thrombolysis, coronary reperfusion, myoglobin, creatine kinase-MB.

## Introduction

Intravenous thrombolysis is the treatment of choice for patients presenting with chest pain and electrocardiographic changes suggestive of acute myocardial infarction<sup>[1,2]</sup>. However, in approximately 30% of patients reperfusion of the infarct-related artery fails<sup>[3,4]</sup>. These patients have increased morbidity, an increase in infarct size and decreased left ventricular function with a lower ejection fraction compared to patients with a patent infarct-related artery<sup>[5,6]</sup>. Aggressive invasive procedures with acute coronary angiography followed by percutaneous transluminal coronary angioplasty (PTCA) is not

universally available and is of no benefit for patients who have a patent infarct-related artery after intravenous thrombolytic therapy<sup>[7]</sup>. Therefore, a rapid and easy to perform non-invasive diagnostic test is required to identify patients who could be candidates for additional intravenous thrombolytic treatment or acute PTCA following failed thrombolysis<sup>[8,9]</sup>.

Previous investigations in patients with acute myocardial infarction, treated without thrombolysis, have compared changes in serum myoglobin with changes in creatine kinase and creatine kinase-MB. An increase in serum myoglobin could be detected earlier and after a smaller amount of myocardial necrosis than an increase in serum cardiac enzymes<sup>[10,11]</sup>. Thrombolytic therapy with documented patency of the infarct-related artery accelerated the release of myoglobin and creatine kinase-MB into the blood compared to conservative treatment<sup>[12,13]</sup>. Coronary reperfusion can be identified in the early hours after thrombolytic therapy by various kinetics of the myoglobin and creatine kinase-MB time-concentration curves<sup>[12,14–19]</sup>.

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The aim of this investigation was to compare the time-concentration curves of serum myoglobin and creatine kinase-MB after intravenous thrombolysis in patients with acute myocardial infarction, and to evaluate the time window for, and the accuracy of, changes in serum myoglobin when used as an early and simple non-invasive diagnostic test to identify patients with and without coronary reperfusion.

## Methods

### *Patient population*

The study comprised 63 patients with acute myocardial infarction. Intravenous and/or intracoronary thrombolytic therapy was given to 52 consecutive patients transferred to the Interventional Cardiac Catheterization Laboratory, Duke University Medical Center, U.S.A., during a 6-month period. These patients had the status of the infarct-related artery determined by acute coronary angiography. An additional 11 consecutive acute myocardial infarction patients not treated with thrombolysis were included to provide a sufficient number of control patients. Spontaneous coronary reperfusion in these patients was excluded by pre-defined electrocardiographic criteria: <20% decrease in ST segment elevation during the first 4 h after admission<sup>[8,20]</sup>. A control group of acute myocardial infarction patients with angiographically documented persistent coronary occlusion could not be identified at the time of this investigation, because it was judged improper not to attempt rescue angioplasty.

Inclusion criteria for all patients were nitroglycerin-resistant chest pain of >30 min, but less than 6 h duration and ST elevation  $\geq 0.1$  mV in at least two contiguous ECG leads. Exclusion criteria were the usual contraindications to thrombolytic therapy or left bundle branch block.

All patients gave written or verbal informed consent to participate in the protocols which were approved by the local ethics committee.

### *Thrombolytic treatment*

The intravenous thrombolytic therapy differed according to local practice and was 1.5 million IU of streptokinase, 100 mg of tissue plasminogen activator, 3 million IU of urokinase, or combinations of the latter two.

### *Reperfusion status*

Reperfusion status in the thrombolytic treated patients was evaluated after coronary angiography according to the principles in the Thrombolysis in Myocardial Infarction Trial (TIMI): TIMI grade 0-1: no perfusion or penetration without perfusion of contrast through the occluding thrombus; TIMI grade 2-3: partial or

complete perfusion distal to the obstruction<sup>[21]</sup>. All films were interpreted by two angiographic readers who were unaware of the results of the serum analysis. TIMI grade 3 flow was found on the initial coronary angiogram in 28 patients and TIMI grade 2 in four patients; after rescue percutaneous transluminal coronary angioplasty (PTCA), TIMI grade 3 was achieved in an additional 12 patients and TIMI grade 2 in five. Because patients with TIMI grades 2 and 3 flow produced similar time-concentration curves of serum myoglobin, with an early peak value indicative of coronary reperfusion<sup>[13,14]</sup>, they were all considered as having undergone reperfusion.

### *Patient groups*

Of the 52 angiographically evaluated patients, 49 had coronary reperfusion (TIMI 2-3 flow) after either intravenous thrombolysis (n=32) or acute PTCA (TIMI 0-1→2-3) (n=17). The three patients in whom the infarct-related artery remained occluded after acute intervention were grouped with the control patients. Thus, the reperfusion group consisted of 49 patients and the no reperfusion group of 14 patients.

### *Serum analysis*

In the Interventional Cardiac Catheterization Laboratory, serum was collected for myoglobin analysis every 15 min, then every 2 h for 12 h and subsequently every 4 h up to 24 h after onset of symptoms. In patients who had conservative treatment serum was collected every 2 h for 10 h and subsequently at 14, 18, 24, 32, 40 and 48-h after admission. All serum specimens were frozen and stored for later analysis at the research laboratory, Medical Department B, Rigshospitalet, Denmark. Myoglobin was analysed using a radioimmunoassay technique (NOVO, Denmark), and creatine kinase-MB concentrations by the enzyme-linked immunosorbent assay (ELISA) technique (NOVO, Denmark).

### *Data analysis*

The time-concentration curves of serum myoglobin and creatine kinase-MB were constructed by calculating the mean serum value in different time intervals depending on the frequency of serum samples (see above). The appearance rate for myoglobin was calculated as the concentration at 2 h after onset of intravenous or intracoronary thrombolytic therapy, or 2 h after admission to the CCU in patients given conservative therapy, divided by baseline values ( $Mb_2/Mb_0$ )<sup>[17]</sup>. Since small myocardial infarcts may result in different serum kinetics of myoglobin, a pre-defined limit of serum myoglobin at 2 h was defined. Smaller infarcts were separated from moderate to larger at a serum myoglobin level of

**Table 1** Baseline characteristics. Values are expressed as medians (interquartile range)

	Reperfusion group (n=49)	No reperfusion group (n=14)	P
Age	59 (range 35–79)	59 (range 44–70)	ns
Males (%)	76	86	ns
Infarct location			
anterior/inferior	32/17	4/10	ns
Time to intervention from onset of symptoms (min)	135 (95–173)	180 (125–255)	ns
Time to reperfusion from onset of symptoms (min)	296 (244–348)	—	—
Time to reperfusion from onset of thrombolytic therapy (min)	146 (108–203)	—	—

200  $\mu\text{g}\cdot\text{l}^{-1}$ . The area under the myoglobin time-concentration curve (AUC) was used as an estimate of infarct size.

### Statistical analysis

Continuous variables are presented as medians (interquartile range). Standard errors of the mean (SEM) are marked on the curves. Mann-Whitney rank sum test was used for comparisons between groups; *P* values <0.05 ( $2 \times a$ ) were considered significant.

## Results

Baseline characteristics for the reperfusion and the no reperfusion groups are presented in Table 1.

### Time-concentration curves of serum myoglobin and creatine kinase-MB in the reperfusion group (Fig. 1)

Vessel opening in the 49 patients in the reperfusion group, as demonstrated by angiography, occurred at <146 (108–203) min (2.4 h) after onset of initial thrombolytic therapy. Peak serum myoglobin was reached earlier than peak serum creatine kinase-MB, 178 min (115–194) vs 550 min (311–728), (2.9 h vs 9.2 h),  $P < 0.0001$ . By the time serum creatine kinase-MB reached its peak value, serum myoglobin had almost returned to its baseline value. In patients without reperfusion the creatine kinase-MB peak value appeared significantly later (550 (311–728) min vs 1080 (1040–1440) min),  $P < 0.0001$ .

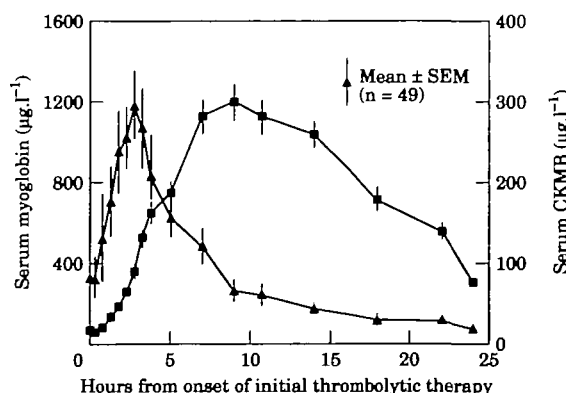
### Time-concentration curves of myoglobin in the reperfusion and no reperfusion groups (Fig. 2(a))

The mean myoglobin time-concentration curve was significantly different for patients with reperfusion

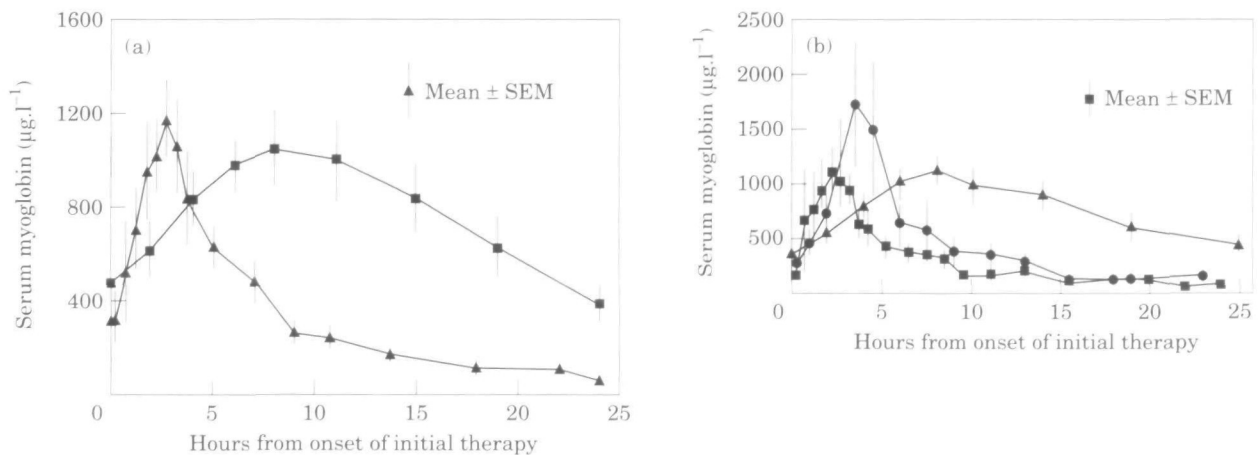
compared with those with no reperfusion; the appearance rate ( $\text{Mb}_2/\text{Mb}_0$ ) was higher, 4.0 (2.0–10.5) vs 1.6 (1.2–2.2),  $P = 0.006$ ; the time to peak was shorter, 178 min (115–216) vs 480 min (330–660), (2.9 h vs 8.0 h),  $P < 0.0001$ ; and AUC (infarct size estimate) was smaller, 5843 (3316–10 369) vs 12 614 (8979–19 731)  $\mu\text{g}/\text{l}$  h,  $P < 0.001$ .

### Time-concentration curves of myoglobin in patients with early reperfusion (TIMI 2–3) and in patients with delayed reperfusion (TIMI 0–1 → 2–3) (Fig. 2(b) and Table 2)

Figure 2(b) illustrates the effect of delayed coronary reperfusion using rescue-angioplasty, compared to early successful intravenous thrombolytic therapy. It appears that the group in which TIMI 2–3 flow was only achieved after additional intracoronary treatment have a later and augmented peak serum myoglobin. This group displays a time-concentration curve mid way between the early successful intravenous thrombolysis group and



**Figure 1** Mean time-concentration curves of serum myoglobin (▲) and creatine kinase-MB (■) in patients in the reperfusion group (n=49). Time 0 is the time of onset of the initial thrombolytic therapy.



**Figure 2(a)** Mean time-concentration curves of serum myoglobin in patients in the reperfusion (▲) and in the no reperfusion (■) groups. Time 0 is the time of onset of the initial thrombolytic or placebo therapy **(b)** mean time-concentration curves of serum myoglobin in patients with initially successful intravenous thrombolysis (TIMI 2-3) (■, n=32) and in patients with unsuccessful or no intravenous thrombolysis but successful rescue PTCA (TIMI 0-1 → TIMI 2-3) (●, n=17), and in patients in no reperfusion group (▲, n=14).

the no reperfusion group; however, the appearance rate (estimated by  $Mb_2/Mb_0$ ) and infarct size (estimated by AUC) were not significantly different between patients with early vs delayed coronary reperfusion (Table 2). Patients in the no reperfusion group had a significantly lower appearance rate and a greater AUC (infarct size estimate) compared to patients in the early reperfusion group. Reperfusion could have occurred at any time before angiography in the patients with early reperfusion after intravenous thrombolysis. However, in the patients with rescue PTCA, peak serum myoglobin was observed as early as 53 (14-73) min after vessel opening when flow increased from TIMI 0-1 to 2-3 grade flow.

#### Serum myoglobin for the detection of coronary reperfusion (Table 3, Fig 3)

Table 3 displays the positive and negative predictive values of different characteristics of the time-

**Table 2 Myoglobin appearance rate and area under the time-concentration curve. Values are expressed as medians (interquartile range)**

	$Mb_2/Mb_0$	AUC ( $\mu\text{g/l} \times \text{h}$ )
TIMI 2-3 (n=32)	5.3 (2.1-12.3)**	5664 (3347-24 863)*
TIMI 0-1 → 2-3 (n=17)	3.0 (1.5-5.8)	7781 (3279-16 373)
No reperfusion (n=14)	1.6 (1.2-2.2)	12 614 (8979-19 731)

\* $P=0.02$ , \*\* $P=0.001$ ;  $P$  values represent comparisons with the no reperfusion group.

TIMI 2-3=patients with a patent infarct-related artery after intravenous thrombolysis; TIMI 0-1 → 2-3=patients with failed intravenous thrombolysis but rescue PTCA;  $Mb_2/Mb_0$ =the rise in myoglobin concentration from baseline values to the concentration at 2 h after onset of initial therapy; AUC=area under the time-concentration curve used as an estimate of infarct size.

concentration curve of myoglobin at different times after the onset of thrombolytic therapy. A rise in serum myoglobin >2.4-fold within 2 h after onset of thrombolytic treatment identified reperfusion patients with positive and negative predictive values of 0.94 and 0.44, respectively. In patients with  $Mb_2 > 200 \mu\text{g}$  the predictive value of the negative test increased to 1.00. An observed peak serum myoglobin within 5 h after onset of thrombolytic therapy also predicted coronary reperfusion with a high degree of accuracy.

## Discussion

Early and complete coronary reperfusion limits extension of the infarcted area<sup>[5,22,23]</sup>, improves left

**Table 3 Positive (pos) and negative (neg) predictive values (PV) when different characteristics of the serum myoglobin time-concentration curve is evaluated at different times after onset of intravenous or intracoronary treatment for identification of patients with and without coronary reperfusion**

	PV <sub>pos</sub>	PV <sub>neg</sub>
$Mb_2/Mb_0 > 2.4$	0.94	0.44
$Mb_2/Mb_0 > 2.4$ or $Mb_2 < 200 \mu\text{g} \cdot \text{l}^{-1}$	0.89	1.00
peak Mb < 3 h	0.94	0.40
peak Mb < 4 h	0.95	0.63
peak Mb < 5 h	0.94	0.79
peak Mb < 6 h	0.94	0.79
peak Mb < 7 h	0.90	0.90

Mb=the concentration of myoglobin;  $Mb_0$ =the concentration of myoglobin at baseline;  $Mb_2$ =the concentration of myoglobin 2 h after onset of thrombolytic treatment; peak Mb=peak concentration of myoglobin; PV<sub>pos</sub>=predictive value of positive test; PV<sub>neg</sub>=predictive value of negative test.

ventricular function<sup>[6]</sup>, and reduces early and late mortality<sup>[1,2]</sup>. Reperfusion of the infarct-related artery improves long-term morbidity and mortality even when reperfusion occurs too late to limit infarct size<sup>[2,6]</sup>. In order to maximise the benefits of thrombolytic therapies, the intravenous thrombolytic drugs should be administered promptly, when the acute myocardial infarction diagnosis is probable. Since the majority of patients are treated in local hospitals, or sometimes at the patient's home<sup>[24]</sup>, it becomes important to evaluate the efficacy of the thrombolytic drug by a rapid and an easy to perform and easy to interpret non-invasive diagnostic test. In this way, further revascularization procedures could be limited to patients with failed reperfusion<sup>[8,9]</sup>. It has been reported that patients with failed intravenous thrombolysis can be treated safely with additional intravenous thrombolytic agents, with a resultant significant reduction in infarct size and greater ventricular ejection fraction compared to patients who were given additional placebo treatment<sup>[8]</sup>.

### *Detection of coronary reperfusion*

Non-invasive detection of coronary reperfusion failure must be in time for potential salvage of the myocardium by secondary revascularization procedures. Previously proposed non-invasive methods for detecting the occurrence of coronary reperfusion, by monitoring serum cardiac enzymes, have required an observation period of >12 h<sup>[13]</sup>. This observation time can be shortened using the initial rise in creatine kinase-MB<sup>[19]</sup>, or by computer-calculating the creatine kinase-MB time-activity curve using the appearance rate constant  $k_1$ <sup>[18]</sup>. The observation and analysis times can be further reduced with new laboratory techniques and when monitoring the creatine kinase-MM or creatine kinase-MB isoforms<sup>[25,26]</sup>. It has been suggested recently that the initial rise in serum myoglobin is superior to other serum markers examined for predicting coronary reperfusion after intravenous thrombolysis<sup>[15-17]</sup>. Of the other non-invasive methods for the prediction of coronary reperfusion, the electrocardiographic methods are the most widely used<sup>[20]</sup>, and the newer digital methods, with continuous on-line ST-segment analysis<sup>[27]</sup> could serve as a complementary technique in those patients in whom frequent serum measurements cannot be obtained or where the biochemical results are equivocal<sup>[28]</sup>.

### *The timing of changes in serum myoglobin and clinical implication*

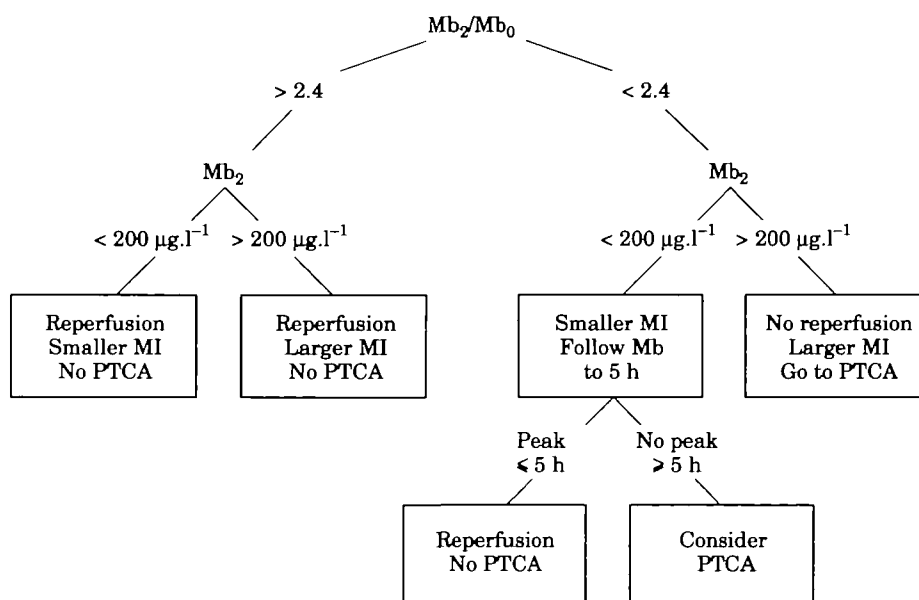
Serum myoglobin can now be analysed within <10 min<sup>[17]</sup>. Serum myoglobin is often elevated, even in the admission blood sample, and this has been used to diagnose acute myocardial infarction very quickly<sup>[11]</sup>. Depending on the duration of symptoms, the baseline values of serum myoglobin could show great variation,

and might confuse the results when the initial rise in serum myoglobin is used as a diagnostic test for coronary reperfusion<sup>[17]</sup>. Also, it is difficult to estimate the best time for collecting the second blood sample for calculating the initial rise in serum myoglobin after initiation of intravenous thrombolytic therapy, because different thrombolytic drugs achieve coronary artery patency at different times after initiation of therapy<sup>[29]</sup>. This has resulted in controversies about the clinical value of measuring the initial increase in any serum marker of myocardial ischaemia for identification of patients with vs without coronary reperfusion after intravenous thrombolytic therapy<sup>[30]</sup>. The present study imitates the clinical situation, because in most patients the exact time of the occurrence of coronary reperfusion is unknown, although whether or not the patient had been reperfused could be documented. The previously described time indexes and cut-off values for calculation of the initial myoglobin ratio ( $Mb_2/Mb_0 > 2.4$ )<sup>[12,17]</sup> were judged proper to use in our study, because the average time to peak serum myoglobin was <3 h after onset of initial thrombolytic treatment, and <1 h after verified coronary reperfusion. With these time indexes, blood collection must be performed frequently, for example every 0.5–2 h if the initial rise or the peak value of serum myoglobin is not to be missed.

### *A comprehensive algorithm based on measurements of serum myoglobin for detection of patients with coronary reperfusion*

The usual cut-off for diagnosing an acute myocardial infarction is a serum myoglobin value of 100–120  $\mu\text{g} \cdot \text{l}^{-1}$ <sup>[10,11]</sup>. In the absence of reperfusion, a diagnostic level of serum myoglobin of >100  $\mu\text{g} \cdot \text{l}^{-1}$  is detectable 1–2 h after symptom onset<sup>[10,11]</sup>. In patients with reperfusion, a rapid rise with very high levels of serum myoglobin (500–5000  $\mu\text{g} \cdot \text{l}^{-1}$ ) are generally detected within 1 h after onset of thrombolytic treatment<sup>[12]</sup>.

We evaluated our acute myocardial infarction patients at 2 h after initiation of thrombolytic therapy or after conservative treatment, about 5 h after symptoms onset. At this time, patients with no reperfusion often have a serum myoglobin >200  $\mu\text{g} \cdot \text{l}^{-1}$  despite its relatively slow rise, and because of the developing infarct size following several hours of coronary occlusion. Patients with initial TIMI grade 3 reperfusion sometimes develop very small infarcts (serum myoglobin <200  $\mu\text{g} \cdot \text{l}^{-1}$ ) and therefore, might not produce a rapid rise in serum myoglobin ( $Mb_2/Mb_0 < 2.4$ ) after initiation of thrombolytic therapy and thus might be identified as not having reperfused (false negative). These false-negative patients with small infarcts secondary to reperfusion could be detected using a cut-off value of serum myoglobin <200  $\mu\text{g} \cdot \text{l}^{-1}$  at 2 h after initiation of therapy. The evaluation of the raw value of serum



**Figure 3** Flow diagram for evaluation of patients for further revascularization therapy after initial thrombolytic therapy. Mb<sub>0</sub>=Serum myoglobin at start of thrombolytic therapy; Mb<sub>2</sub>=serum myoglobin 2 h later; MI=acute myocardial infarction; PTCA=therapy with balloon angioplasty or other invasive strategy to reestablish flow in the infarct related artery.

myoglobin and the myoglobin ratio at 2 h after initiation of thrombolytic therapy documented reperfusion in 100% of the patients in the reperfusion group, but it also identified six patients with false-positive tests out of 14 patients with no reperfusion; the predictive value of a positive test was 0.57 and of a negative test it was 1.00. In this way a negative test at 2 h after initiation of thrombolytic therapy unequivocally identified patients without coronary reperfusion.

An observed peak serum myoglobin <5 h after onset of intravenous or intracoronary thrombolytic treatment increased the predictive value of a positive test to 0.94. A later peak of serum myoglobin would indicate no reperfusion, but in a few patients (n=3) it indicated late reperfusion. However, these patients would have needed earlier revascularization to salvage the myocardium.

### *Limitations of the study*

At the time of this study, no population could be found in whom coronary occlusion was verified angiographically. Therefore, no coronary angiograms were performed in most of the patients in the no reperfusion group. Even in the absence of thrombolytic therapy, there was a small chance that a few of these patients could have experienced spontaneous reperfusion. However, by evaluating them with a strict<sup>[20]</sup>, non-invasive, independent and previously described electrocardiographic index, which identifies patients with and without

coronary reperfusion, the likelihood of not having identified patients with spontaneous reperfusion is minimized.

A second limitation is that patients in the conservative therapy control group had less frequent blood sampling in the earliest phase. This could be of concern had the first or second blood sample expressed the peak value of serum myoglobin. However, because peak serum myoglobin is delayed when no reperfusion occurs, and because all these patients had an initial serum sample and a serum sample at 2 h after admission, the Mb<sub>2</sub>/Mb<sub>0</sub> ratio could be accurately calculated in these patients. In this way, the less regular serum sampling procedure is unlikely to have had an impact on the results of the study.

There is controversy about patients with TIMI grade 2 reperfusion. When comparing the clinical outcome evaluated by global ejection fraction, peak enzyme values, final QRS score and a morbidity index, there was no difference between these patients and those with no reperfusion<sup>[31]</sup>. In our study, patients with TIMI grade 2 reperfusion had a significantly larger infarct than those with TIMI grade 3 reperfusion,  $P=0.05$ , and this might explain why the clinical outcome in patients with TIMI grade 2 reperfusion was previously found to be poor. In other studies<sup>[31]</sup>, as in ours, patients with TIMI grade 2 reperfusion showed a rapid rise and fall in serum myoglobin levels shortly after initiation of thrombolytic treatment, with a shorter time to peak value. The suggested reperfusion indexes did not identify patients with TIMI grade 3 vs TIMI grade 2 reperfusion.

## Conclusion

This investigation established an index of coronary reperfusion based on identification of a rapid rise in serum myoglobin and an evaluation of the raw value of serum myoglobin 2 h after initiation of thrombolytic therapy. Patients with  $Mb_2/Mb_0 > 2.4$  are most likely to have had successful coronary reperfusion after intravenous thrombolytic therapy and need no further acute invasive therapy. Patients who are likely to have large infarcts (since  $Mb_2 > 200 \mu\text{g/l}$ ) and no reperfusion (since  $Mb_2/Mb_0 < 2.4$ ) should be treated with further revascularization. Patients with  $Mb_2 < 200 \mu\text{g.l}^{-1}$  may be followed with hourly serum sampling for identification of a peak value. If a peak value of serum myoglobin is not present within  $< 5$  h, further reperfusion should be considered.

The serum sampling intervals are realistic and the time frames combined with the accuracy of the test are superior to standard measurements of serum creatine kinase-MB. Within 2–5 h of thrombolytic treatment, the myocardium may still be salvageable if the patient is directed towards secondary intervention with additional intravenous thrombolytic treatment or subacute PTCA. The newer assays for quantification of serum myoglobin may be performed rapidly (within 10 min), and using the above proposed non-invasive diagnostic method, the results are easy to interpret. A combined approach of monitoring the raw value and the initial rise and the peak value of serum myoglobin, added to online monitoring of the electrocardiographic ST-segment elevation, should provide a comprehensive method for early determination of the success or failure of intravenous thrombolytic therapy.

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